2) Examples 1 through 7, pages 7 through 17, which describe precise defining properties of malignin and other Recognins as observed with reference to their specific antibody, antimalignin (anti-Recognin) antibody, so that both the chemical nature and properties of the substance to be used as a vaccine are defined. One can only claim to have a "vaccine" if there is evidence of its specific antibody or antibodies. The properties in Examples 1 through 7 in terms of generation of and reaction with the vaccine's specific antibody are critical to the concept of and definition of a vaccine, and therefore to the uniqueness of the present invention, as further discussed below.

3) Patent #4,976,957 which describes the methods of preparing malignin and other Recognins and adds further to the details of the specification of how to make the vaccine.

4) Example 8 in which the method of administering the vaccine is detailed.

The Examiner states: "Because patients diagnosed with cancer already have increased serum levels of anti-Recognin antibodies, as disclosed in the specification, it is not predictable whether enhancing these antibody levels by administering a Recognin vaccine would be effective in treating the cancer. " It is fully expected from three lines of evidence that enhancement of antibody concentration would occur with 'booster' doses of vaccine, and that this increase in antibody concentration would be beneficial, that is, result in improved survival of the cancer patient. Thus,

1) the immunization with 'booster' doses of the antigen (vaccine) in mice and in rabbits *in vivo*, produces increased antibody response[9] (reference cited in application, page 7);

2) in the production of the antibody with human B lymphocytes *in vitro*, a boost invariably occurs over baseline production of antimalignin antibody when the animal or B cells are challenged with antigen [6,8,9]. Therefore the administration of Recognin

vaccine is reliably expected to produce the same boost in antibody production over and above that which the individual is producing at the time. Furthermore

3) such higher levels of antimalignin have in fact already been shown to be quantitatively related to the patient's survival. The Examiner's attention is respectfully drawn to application page 5, lines 3 through 7, which state: "Anti-Recognin, --------- is quantitatively related to survival in patients[7-13]." The studies referred to have shown conclusively, with actuarial survival methods, at probability levels below $p<.0001$, that the length of survival of known cancer patients is quantitatively related to the absolute concentration of serum anti-recognin antibody, that is, the greater the concentration of the antibody, the longer the survival of the patient.

These data by themselves, did not compel the conclusion that a recognin vaccine might be useful. However, when these data are read in the light of the new findings by the Applicant specified in this application, that is, that this antibody increases in concentration in pre-cancer individuals as the cancer risk increases, and that this antibody is in fact cytotoxic or cytostatic to cancer cells, then the possibility of a vaccine presented. Hence, 1) anti-Recognin antibody increases in concentration in non-clinical-cancer individuals as they increase in age towards the period of greater risk of developing cancer (Example 7, and Figure 3); and 2) anti-Recognin antibody is cytotoxic or cytostatic to cancer cells at the very low concentrations of picograms per cell (Example 6 and Figure 2). Therefore , in the light of the known data and the unique clinical data described above, one of ordinary skill in the art could predict that the claimed vaccine would sufficiently increase the levels of anti-Recognin antibodies to prevent or treat cancer in humans. There is no other such clear definition of a specific antigen <u>together with its specific antibody</u> in patients with cancer, and of the

relevance to survival of the functioning of this immunosurveillance system. As shown below, this demonstration that an antibody is produced is critical to the use of the term vaccine.

Claim 1 was rejected under 35 U.S.C. § 102(b) as being anticipated by Cantrell. Applicant respectfully wishes the Examiner to note that although Cantrell uses the term "vaccine", nowhere are data given in his patent which indicate that what is injected by Cantrell in fact acts like a vaccine and produces specific antibody which antibody kills or suppresses cancer cells. Simply using the term "vaccine" does not make it so. Since there are literally thousands of substances which are known to the art which when injected into animals kill or suppress the growth of cancer cells, and do so by dozens of different methods, the fact that what is injected by Cantrell has anti-cancer effects in no way justifies the use of the term "vaccine" since no evidence is presented that any immune reaction was involved in the alleged anti-cancer activity, i.e, there is no evidence that antibody was produced, let alone that such antibody had a negative effect on the cancer cells, and these are essential defining conditions of a vaccine.

In contrast, the Applicant details the evidence in all the Examples in the Applicant's application, which demonstrate clearly that what the Applicant is defining is an immunological reaction, and that the anti-Recognin antibody "has been isolated from human serum[6], produced in mouse monoclonal form[9], and produced *in vitro* by human lymphocytes challenged by the antigen Recognin[8]; and in all these cases has been shown to be an IgM[8]."(Application page 6, lines 12 through 15).

What Cantrell injects, which he claims to be "antigens" (in fact, "whole cells, fractions of cells or extracts of tumor cells--") (Cantrell, Column 3, lines 39 and 40), are in no way characterized to be "antigens" since they are neither defined as to

composition nor shown to produce antibodies. "The refined" material injected by Cantrell is claimed to be an endotoxin MPL which by itself may well have anti-cancer effects, but which is claimed by Cantrell to be "detoxified", by which is meant it is less toxic although still retaining endotoxin activity (Column 3, lines 49-53; Column 4, lines 42 to 47). In fact this material is claimed by Cantrell not to be an antigen, but to be an adjuvant, that is something which assists an immunological reaction but itself has not the specificity or function of an antigen (Column 4, lines 48 to 53).

Whatever the action(s) of what Cantrell injects, it is not claimed by Cantrell to be a general action applicable to all cancers, regardless of cell type of origin as is the case in the Applicant's application.

Whatever is injected, "whole cells, fractions of cells or extracts of tumor cells" provide for thousands of potentially toxic substances which could account for the anti-tumor effects in mice obseved by Cantrell. Nowhere is an immune mechanism demonstrated by Cantrell.

Therefore the patent of Cantrell is not relevant to the present Application since Cantrell does not teach anything about tumor "antigens" or tumor "vaccines". He may be teaching about adjuvants, but these are not clearly individually controlled in any of his experimental examples, either from each other, or from the thousands of proteins and other potentiallly toxic substances injected in the mixtures he calls "vaccine".

Claim 1 was rejected under 35 U.S.C. § 102(e) as being anticipated by Rapp. The Examiner states that "Rapp teaches the administration of oncoproteins induce an anti-oncoprotein immune response to neutralize cancer". Rapp *asserts* (italics the Applicant's) that oncoproteins may be used as immunogens but gives no evidence that an immune response has been observed. In comparison to Cantrell, Rapp at least defines what he is injecting, that is, raf protein, although data indicating degree of

purity are not given. However nowhere does Raff give any data to indicate that raf protein or anything else that he is injecting, is in fact acting as an immunogen; that is, there is no evidence that specific antibody is produced. Therefore the same objection cited by the Applicant with regard to Cantrell's patent applies to Rapp as well. That is, something is injected which apparently results in slight retardation of time of onset of the tumors in mice but has no effect on mortality of the mice. There are no controls cited for injection of other proteins, or for injection of Freund's adjuvant alone, both of which are known to produce these slight non-definitive effects observed in Rapp.

Again, a vaccine is not made by the mere naming the material a "vaccine", unaccompanied by any evidence of an immune response as defined by specific antibody response to the putative antigen. The theory that there should be specific tumor antigens and antibodies, that an antibody response should be observed in tumor development, and that administration of the specific tumor antigens (vaccine) should protect the animal or person against cancer much as such injection of bacterial specific proteins actually protect individuals from bacterial invasion, with the production of attendant specific cytotoxic antibodies being measurable, have been deemed reasonable hypotheses by all skilled in the art since the beginning of this century when they were first enunciated by Ehrlich. The theory got a renewed boost in 1959 when Lewis Thomas proposed immunosurveillance as the normal mechanism of destroying tumor cells which formed throughout our lifetimes. But as recently confirmed by Lewis Thomas, there was no direct evidence of any of the above in human cancer until malignin and anti-malignin antibody were discovered and defined, shown to increase when clinical cancer appeared, to return to normal when it was successfully treated, and to have the success of the outcome of treatment relate directly and quantitatively to the concentration of antimalignin antibody in serum, then,

critically for the possibility of a vaccine, the antibody was shown here to be cytotoxic/cytostatic to cancer cells at the low doses of picograms/cancer cell, and to increase with age in normal individuals as cancer risk increased. The reality and specificity of the antigen and the antibody, of the immunogenicity of the antigen, and of the use of the antigen as vaccine, have only been demonstrated with malignin-antimalignin. The fact that the immune epitopes are shared by the Recognins makes the antibody response a general one, that is it is not necessary to know which cell type is involved. In both Cantrell and Rapp, this is not the case; no antibody response is demonstrated.

Claim 2 was rejected under 35 U.S.C. §103 as being unpatentable over Cantrell or Rapp in view of Bogoch et al and Bogoch et al. Since the Applicant has shown that neither Cantrall nor Rapp has given any immune data which indicate that either tumor associated substances or oncoproteins, respectively, have any demonstrated properties in terms of production of antibody to qualify them as a immunogens, let alone as vaccines, and since the effects observed by injecting each could well be due to non-immune anti-cancer activity, neither patent represents a patent of a cancer vaccine, and therefore neither is relevant to the present Application on Recognin vaccines. Therefore, the fact that Bogoch et al (1980) and Bogoch et al (1991) teach that Recognin is a tumor associated antigen and an oncoprotein is correct but irrelevant to the Applicant's present claims. That is, being a tumor associated substance or an oncoprotein does not determine the fact that Recognin is a vaccine. There are many tumor markers and there are many oncoproteins but to the Applicant's knowledge, none other than the Recognins have the demonstrated immune properties that permit them to be assigned the function and role of vaccines. Since one of ordinary skill would not know of the Applicant's recent discovery, that is

that antimalignin antibody is a cytotoxic/cytostatic antibody which increases in concentration in normal humans as the risk of cancer increases, they would not expect that Recognins could be vaccines any more than they would expect the other several dozen tumor markers and oncoproteins, which have not had defined the full range of immune (antigen-antibody) properties of the Recognins, could function as vaccines.

On the basis of the above amendments and remarks, reconsideration and allowance of claims 1 and 2 are believed to be warranted and are respectfully requested.

Respectfully submitted,

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